REMARKS

I. The Claims

Claims 1-22 are pending and claims 1-12 are presently under examination. Claims 13-22 are presently withdrawn as being directed to non-elected inventions.

Claims 1, 7 and 9 have been amended herein. Support for the amendment of claim 1 is found in originally filed claim 1. Each of the claims 7 and 9 has been amended to recite the ATCC Accession No. for Applicants' deposit of the hybridoma producing antibody E4B9.

No new matter has been added by any of the amendments of the claims and specification made herein.

II. Elections/Restrictions

Applicants acknowledge and thank the Examiner for rejoinder of claims 8 and 9. (Office Action, ¶6.)

III. Objections to the Specification

(A.) The Abstract of the disclosure was objected to under to MPEP 608.01(b) because it was improperly titled "ABSTRACT OF THE INVENTION." (Office Action, ¶9.)

In accordance with the Examiner's suggestion for remedying the objection, the title of the Abstract has been amended herein to "ABSTRACT." Accordingly, withdrawal of the objection is respectfully requested.

(B.) The Examiner objected to a purported incongruity in the description of "peptide 1" between paragraph nos. [0094] and [0028] of the originally filed specification (as numbered in corresponding U.S. publication no. 2002/0160003). (Office Action, ¶10.)

Applicants first wish to point out that in paragraph no. [0028] in the sentence containing "Peptides 1...2...," what is presented is a listing by number of the peptides discussed *in that sentence*, not necessarily their SEQ ID NOS, which are explicitly specified in the next sentence of the paragraph. In the first line of paragraph no. [0094], "peptide 1" is used to describe the amino acid region of the epitope and does not refer to the peptide of SEQ ID NO: 1, which is a peptide used to generate antibodies against said region.

To further address the Examiner's concern, Applicants have amended paragraph no. [0094] of the specification to delete "(peptide 1)."

In view of the above, Applicants submit that the alleged incongruity has been rectified and respectfully request withdrawal of the present objection to the specification.

III. Claim rejections under 35 U.S.C. §112, second paragraph

(A.) Claims 1-12 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for reciting that the claimed antibody or fragment may bind a site "contained within a portion of the VE-cadherin, which differs from the corresponding portion of the 'native VE-cadherin'" and thus, according to the Examiner, it is not clear whether the antibody binds VE-cadherin. (Office Action, ¶11(a.).)

The present rejection is overcome for the following reasons.

The rejection has been rendered moot by the amendment of independent claim 1 herein to eliminate the alternative binding specificities that were previously recited. As presently amended, claim 1 recites:

> 1. An isolated antibody or isolated antibody fragment capable of specifically binding to a site on mouse or human VE-cadherin, said site being within the about first 15 N- terminal amino acids of domain 1 of the VE-cadherin,
>
> wherein said antibody or said antibody fragment is capable of inhibiting VE-cadherin mediated adherens junction formation in vitro but does not exert any significant or substantial effect on paracellular permeability in vitro.

Accordingly, the grounds on which the rejection was based are no longer present in the claim.

In view of the above, withdrawal of the present claim rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

(B.) Claims 7, 9 and 12 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for using the laboratory designation EB49 as the sole means of identifying the particular antibody. (Office Action, ¶11(b.).)

The present rejection is overcome for the following reasons.

In accordance with the Examiner's suggestion for overcoming the present rejection, Applicants have amended claim 7 herein to recite the ATCC Accession No. for antibody EB49, namely "PTA-1618."

In view of the above, withdrawal of the present claim rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

IV. Claim rejections under 35 U.S.C. §112, first paragraph, Written Description

(A.) Claims 1-12 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. (Office Action, ¶12 – page 5, l. 10 to page 10, l. 31.) Specifically, the Examiner asserted that the written description is inadequate because "the claims are directed to antibodies or fragments thereof that bind *any* one member of genus of structurally and/or functionally varying 'VE-cadherin" polypeptides, including *but not limited to* human VE-cadherin and mouse VE-cadherin." (Office Action, page 6, l. 27-28 and page 5, l. 10 to page 10, l. 31. generally.)

The present rejection is overcome for the following reasons.

Independent claim 1 has been amended herein to recite that the claimed antibody or antibody fragments specifically bind "to a site *on mouse or human VE-cadherin*, said site being within the about first 15 N- terminal amino acids of domain 1 of the VE-

cadherin" (emphasis added), and the previously recited, alternative binding specificities have been deleted from the claim. The crux of the Examiner's argument was that the claims included, without adequate written description, antibodies specifically binding a broad genus *beyond* mouse and human VE-cadherin. Accordingly, the amended claims now recite a scope of invention that, consistent with the Examiner's analysis, was fully and adequately possessed by Applicants.

In view of the above, withdrawal of the present claim rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

(B.) Claim 9 was rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description since, according to the Examiner, the specification does not adequately support hybridomas producing antibody E4B9 *other than* the hybridoma having ATCC Accession No. PTA-1618. (Office Action, ¶12 – page 11, l. 1-7.)

The present rejection of the claims is overcome for the following reasons.

Claim 9 has been amended herein to recite that the subject hybridoma is that designated by ATCC Accession No. PTA-1618. Accordingly, claim 9 as amended is adequately described.

In view of the above, withdrawal of the present claim rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

V. Claim rejections under 35 U.S.C. §112, first paragraph, Enablement

(A.) Claims 1-6 and 8-12 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled (Office Action, ¶13.) Specifically, the Examiner asserted that:

> [t]he specification, **while being enabling for making and using** the hybridoma deposited under ATCC accession number PTA-1618 and the antibody produced by said hybridoma, an antibody or antigen binding fragment thereof that binds human VE-cadherin or mouse VE-cadherin, a hybridoma producing said antibody that binds human VE-cadherin or mouse VE-cadherin, and a composition

> comprising any of said antibodies or antigen binding fragments thereof, **does not reasonably provide enablement for making or using** an antibody or antibody fragment that binds a site on any of a plurality of "VE-cadherin" polypeptides, an antibody or antibody fragment that binds a peptide or polypeptide comprising the amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3, a hybridoma producing any of said antibodies or antibody fragments, or a pharmaceutical composition comprising any of said antibodies or antibody fragments.
>
> (Office Action, page 11, l. 9-20; underline added.)

The present rejection of the claims is overcome for the following reasons.

As previously pointed out hereinabove, independent claim 1 has been amended to recite only antibodies or antibody fragments that bind "to a site *on mouse or human VE-cadherin*, said site being within the about first 15 N- terminal amino acids of domain 1 of the VE-cadherin." Accordingly, as pointed out by the Examiner in the excerpt above, the subject matter of presently amended claim 1 and its dependent claims is enabled.

In view of the above, withdrawal of the present claim rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

(B.) Claim 9 was rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled since, according to the Examiner, it is not clear how to make a hybridoma *other than that already made by Applicants, i.e., ATCC Accession No. PTA-1618,* that produces the antibody EB49 of base claim 7. (Office Action, ¶13 – page 22, l. 1 to page 23, l. 26)

The present rejection of the claims is overcome for the following reasons.

Claim 9 has been amended to recite that the subject hybridoma is that designated by ATCC Accession No. PTA-1618. As indicated by the Examiner, said amendment overcomes the present rejection of claim 9.

In view of the above, withdrawal of the present claim rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

VI. Claim rejections for anticipation under 35 U.S.C. §102

VI(A.) Applicable law and procedure

The applicable law and procedure regarding anticipation under 35 U.S.C. §102, particularly with respect to inherency, is reprinted in pertinent part below.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).
> **MPEP 2131**
>
> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)
> **MPEP 2131.01** (Emphasis added.)
>
> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)
> **MPEP 2112 (IV.)** (Emphasis added.)
>
> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)
> **MPEP 2112 (IV.)** (Emphasis *in original*.)
>
> "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on

'prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

MPEP 2112 (V.) (Emphasis added.)

[W]e turn to the decision in In re Brown , 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972) wherein, at 59 CCPA 1041, Judge Baldwin, delivering the court's opinion, explains:

"We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable.

Ex Parte Grey, 10 USPQ2D 1922, 1924 (BPAI 1989). (Emphasis added.)

Appellants' attention is invited to the decision in In re Best , 562 F.2d 1252, 195 USPQ 430 (CCPA 1977), wherein the court held that the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product.

Ex Parte Grey, 10 USPQ2D 1922, 1925 (BPAI 1989). (Emphasis added.)

VI(B.) Claim rejections under 35 U.S.C. §102(b)

Claims 1-6 and 12 were rejected under 35 U.S.C. §102(b) as allegedly being inherently anticipated by Lampugnani et al. (1992) J. Cell Biol. 118(6):1511-1522 ("Lampugnani"). (Office Action, ¶15.) Specifically, the Examiner has asserted that:

Although Lampugnani et al. does not expressly teach the disclosed antibodies or fragments thereof are capable of inhibiting VE-cadherin mediated adherens junctions formation without exerting significant or substantial effect on paracellular vascularity in vitro and/or vascular permeability in vivo, such specific properties of antibodies are deemed inherent properties of the claimed antibodies or fragments thereof. Accordingly, because the disclosed antibodies specifically bind to a peptide comprising the amino acid sequence of SEQ ID NO: 3, the prior art teaches antibodies that are structurally and functionally indistinguishable from the claimed antibody or antibody fragment. Notably, the Office does not have the facilities for examining and comparing Applicant's product with a product disclosed by the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed product is

> different from the product taught by the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and Ex parte Gray, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).
> (Emphasis added.)

The present rejection of the claims is overcome for the following reasons.

Contrary to the Examiner's assertion, Lampugnani does not teach "antibodies that are structurally and functionally indistinguishable from the claimed antibody or antibody fragment."

The presently amended claims recite an isolated antibody or antibody fragment capable of specifically binding to "a site on mouse or human VE-cadherin, said site being within the about first 15 N-terminal amino acids of domain 1 of the VE-cadherin.

Lampugnani teaches that: (a.) antibody 7B4 of that reference was raised directly against human umbilical vein endothelial cells according to the method of Piggot et al. (1991) J. Immun. 147(1): 130-135 (newly disclosed in accompanying IDS; see Lampugnani, p. 1512, L-col., 7-10); (b.) mAb 7b4 recognizes VE-cadherin (a/k/a Cadherin-5; Lampugnani, page 1521, 3rd full paragraph); (c) the antigen recognized by mAb 7B4 localizes to intercellular borders of endothelial cells (Lampugnani, page 1516, Figure 2); and (d.) mAb 7B4 increases cell permeability even at 100 μg/ml at a minimum incubation time, which continue to rise reaching a plateau at 4 and 6h (Lampugnani, 1518, L-col., l. 3-8).

Thus, Lampugnani does not teach or even suggest that mAb 7B4 binds in or about the first 15 amino acids of VE Cadherin, does not teach a method of producing antibodies that necessarily will bind in or about said 15 amino acids and provides only a remote suggestion (not proof, only inference) by way of the permeability increasing activity that 7B4 is binding the extracellular face of VE-cadherin (versus the intracellular domain). In addition, even assuming for the sake of argument that mAb 7B4 of Lampugnani does bind the extracellular domain of VE-cadherin, Applicants wish to point out that the extracellular domain of VE-cadherin is approximately 500 amino acids in length (see Lampugnani, page 1519, Figure 6.). Thus, there is no suggestion or evidence (intrinsic or extrinsic) whatsoever that mAb 7B4 binds within the presently claimed N-terminal region.

(i.) As pointed out in Section VI(A.) above, Ex Parte Grey, 10 USPQ2D 1922, 1924 (BPAI 1989) requires that there must be at least a ***reasonable*** *appearance* of identity or only very slight difference between the prior art product and the claimed invention to properly lodge a rejection for inherent anticipation. In view of the difference discussed above, Applicants submit that it is not reasonable to assert that the presently claimed invention and antibody 7B4 of Lampugnani are identical or even very slightly different.

Further, in view of the large number of amino acids, approximately 500, in the extracellular domain of VE-cadherin (see Lampugnani, page 1519, Figure 6) and the art-recognized antibody property of binding epitopes of 4 to 8 amino acids in length, it is clear that there are at least several hundred possible extracellular epitopes, but only very few possible in the N-terminal 15 amino acids of domain 1, as presently claimed. Thus, it is not reasonable to presume that mAb 7B4 has CDRs (complementarity-determining regions) imparting binding specificity to the presently claimed N-terminal region and, thus, it is not reasonable to presume that the structure of the presently claimed antibodies is identical with or only very slightly different than prior art mAb 7B4.

Even for these reasons alone, i.e. that the threshold of reasonableness for asserting identity or only very slight different with the prior art product has not been met, the rejection should be withdrawn.

(ii.) In addition, as also pointed out in Section VI(A.) above, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities." MPEP 2112(IV.) As pointed out in Section VI(A.) above, according to Ex Parte Grey, 10 USPQ2D 1925 an applicant may overcome a rejection for inherent anticipation by proving that "the prior art products do not necessarily or inherently possess the characteristics of his claimed product." In addition to not necessarily binding within the presently recited N-terminal region (see (i.) above), the *experimental evidence* presented in Applicants' originally filed specification proves that mAb 7B4 does not necessarily have the functional limitations presently claimed. Specifically, as shown by Example 2 and accompanying Table 1 on pages 23 and 24 of

the originally filed specification, even among monoclonal antibodies raised against the N-terminal 15 amino acid region of VE-cadherin, only a small minority of antibodies obtained, are both capable of inhibiting formation of new adherens junctions (as required by the instant claims) *and* do not cause significant effect of paracellular permeability in vitro (as also required by the present claims). Thus, the 7B4 product of Lampugnani definitively does not necessarily have said presently claimed characteristics, nor would any person skilled in the art be able to recognize that it does have or must have said characteristics.

Even for these reasons alone, and also in combination with the reasons presented in (i.) above, the present rejection should be withdrawn.

(iii.) Antibody 7B4 of Lampugnani also appears to be different from the present invention in that mAb 7B4 increases paracellualar permeability in vitro of a confluent endothelial cell monloayer, while the presently claimed antibody "does not exert any significant or substantial effect on paracellular permeability in vitro."

In view of above, withdrawal of the present of the claims under 35 U.S.C. §102(b) is respectfully requested.

VI(C.) Claim rejections under 35 U.S.C. §102(a)

Claims 1-6 and 12 were rejected as allegedly being inherently anticipated by Corada et al. (1999) Proc. Natl. Acad. Sci. USA (96): 9815-9820 ("Corada (1999)"). (Office Action, ¶16.) Specifically, on page 26 of the Office Action, the Examiner asserted that:

> Corada et al. teaches rat monoclonal and rabbit polyclonal antibodies that specifically bind to mouse VE-cadherin; see entire document (e.g., page 9815, column 2). Corada et al. teaches a fragment of a monoclonal antibody having this binding specificity; see, e.g., page 9815, column 2. Corada et al. teaches compositions comprising these antibodies and a pharmaceutically acceptable carrier or diluent (e.g., water); see, e.g., page 9816, column 1.
>
> Although Corada et al. does not expressly teach that the disclosed polyclonal antibody binds mouse VE-cadherin at a site in the about first 15 N-terminal amino acids of domain 1 of the polypeptide, absent a showing otherwise, the polyclonal antiserum comprises a species of antibody capable of binding to this site. This conclusion is reasonable because a polyclonal antiserum produced against a recombinant fragment of mouse VE-cadherin consisting of the

extracellular domain is expected to comprise antibodies that bind to any and all epitopes (i.e., antigenic determinants) of such a polypeptide.

Although Corada et al. does not expressly teach each of the disclosed antibodies or fragments thereof are capable of inhibiting VE-cadherin mediated adherens junctions formation without exerting significant or substantial effect on paracellular vascularity in vitro and/or vascular permeability in vivo, such specific properties of antibodies are deemed inherent properties of the claimed antibodies or fragments thereof, unless it has been established that the antibodies lack such properties. Corada et al. teaches monoclonal antibodies BV13 and BV14 bind distinct epitopes of mouse VE-cadherin, and while BV13 exerts significant or substantial effects upon vascular permeability in vivo, BVl4 does not; see, e.g., page 9816, column 2; and page 9817, Figure 5. Otherwise, because the other disclosed antibodies specifically bind to a peptide comprising the amino acid sequence of SEQ ID NO: 2, the prior art teaches antibodies that are structurally and functionally indistinguishable from the claimed antibody or antibody fragment; and as explained above, the Office does not have the facilities for examining and comparing Applicant's product with a product disclosed by the prior art in order to establish that the product of the prior art does not possess we same matcrial, structural, and functional characteristics as the claimed product. Again, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed product is different from the product taught by the prior art.

The present rejection of the claims for inherent anticipation by Corada (1999) is overcome for the following reasons.

(i.) Polyclonal Sera of Corada (1999)

With respect to the Examiner's assertion of inherent anticipation by the polyclonal antiserum of Corada (1999), Applicants first wish to point out that presently amended independent claim 1 and its dependent claims recite an "isolated antibody" or "isolated antibody fragment" that has all of the limitations recited in the claim 1. (See listing of claims.) Since, as the Examiner has asserted, a polyclonal serum may be assumed to contain antibodies against all possible epitopes, it cannot be seen how the polyclonal antiserum cited by the Examiner discloses an *isolated* antibody (or fragment) that has the presently recited binding *and* functional limitations. Corada (1999) fails to teach the isolation of any such antibody from the cited polyclonal antiserum.

Further, claims 6-9 and 12 (as dependent on any one of claims 6-9) are not anticipated by the polyclonal sera of Corada (1999) because these claims recite monoclonal antibodies or hybridomas producing monoclonal antibodies. Thus, the cited polyclonal antiserum is not anticipatory.

(ii.) Monoclonal Antibodies of Corada (1999)

The Examiner has acknowledged that antibody BV13 of Corada (1999) "exerts significant or substantial effects upon vascular permeability." (See ¶3 of OA excerpt above). Accordingly, antibody BV13 does not anticipate the present claims. However, the Examiner has asserted that antibody BV14 of Corada (1999) *does* anticipate the present claims because BV14 does not affect permeability. (Id.)

This aspect of the present rejection is overcome for the following reasons.

The Examiner is respectfully directed to Corada et al. (2002) Blood 100 (3): 905-911 ("Corada (2002);" *of record*, page 6 of Notice of References cited.), which characterizes the epitopes recognized by antibodies BV13 and BV14. Specifically, Corada (2002) teaches that antibody BV14 binds an epitope between amino acids 370 and 475. For convenience, the referenced passage of Corada (2002) is reprinted below:

> To identify the epitope of BV13 and BV14, recombinant VE-cad-Ig chimeras were produced.[34] The fragments spanning different extracellular repeats of the protein EC1 (1-148 AA), EC1-2 (1-255 AA), EC1-3 (1-370 AA), EC1-4 (1-475 AA), and EC1-5 (1-592 AA) were tested for their capacity to bind BV13 and BV14 by ELISA assay.[34] As reported in Table 1, BV13 was able to effectively bind all the constructs containing the first aminoterminal repeat EC1, while BV14 bound only constructs containing the EC4 repeat. We concluded that while BV13 binds EC1, BV14 binds to a region located in EC4 and closer to the cell membrane.
>
> Corada (2002) page 909, R-col., under heading "BV14 and BV13 recognize different regions of VE-cadherin extracellular domain."

Accordingly, antibody BV14 fails to anticipate the presently claimed invention because its binding specificity falls outside of the present claim limitation requiring that the antibody or antibody fragment binds an epitope "within the about first 15 N-terminal amino acids of domain 1 of the VE-cadherin." (See presently amended claim 1.)

(iii.) "Other Antibodies" of Corada (1999)

With respect to the Examiner's final assertion in connection with Corada (1999) that "[o]therwise, because the other disclosed antibodies specifically bind to a peptide comprising the amino acid sequence of SEQ ID NO: 2, the prior art teaches antibodies

that are structurally and functionally indistinguishable from the claimed antibody or antibody fragment," (see ¶3 of OA excerpt above), presumably the Examiner is referring to anti-VE-cadherin monoclonal antibodies 13E6 and 13C7 that are described in Figure 1 on page 9816 of Corada (1999).

With respect to mAb 13E6 and mAb 13C7, for the same reasons cited in Section VI(B.) above for mAb 7B4, it is (a.) not reasonable to assume that either of these antibodies is identical or substantially identical to the presently claimed antibodies and (b.) in view of the large number of amino acids of VE-cadherin extracellular domain and overall, it is completely not necessary that either of these antibodies would bind in the first N-terminal amino acids of VE-cadherin, nor would any skilled worker conclude that either does or must do so, and (c.) even if either of these antibodies did bind within the presently claimed region (about first 15 N-terminal amino acids), the experimental evidence presented in Applicants' originally filed specification (Example 2 and Tables 1 and 2) demonstrates that such an antibody does not necessarily have the recited functional characteristics claimed (i.e., preventing formation of new adherens junctions, without substantially affecting permeability by disrupting preexisting ones), nor would any skilled worker conclude that it does or must. Accordingly, there is no anticipation of the presently claimed invention by either of mAb 13E6 or mAb 13C7 of Corada (1999).

In view of above, withdrawal of the present of the claims under 35 U.S.C. 102(a) is respectfully requested.

VIII. Conclusion

Pursuant to this paper, Applicants submit that pending and elected claims 1-12 are in condition for further examination and allowance, which action is hereby requested.

No fees other than those mentioned above should be due in connection with the filing of this paper. If, on the other hand, it is determined that any fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275. Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

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I hereby certify that this document is being electronically transmitted to the Commissioner for Patents via EFS-Web on July 30, 2007.

LUCAS & MERCANTI, LLP

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